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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,521	08/13/2001	Shinji Matsuyama	44324.013100	9592

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	11

DATE MAILED: 07/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/913,521	Applicant(s) MATSUYAMA ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-29 is/are pending in the application.

4a) Of the above claim(s) 4,5,21,22 and 27-29 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3,6-20 and 23-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Objections

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

The claims were presented in the original U.S. stage of the application as claims 1, (2 cancelled), 3, (4 cancelled), 5, 6, 7, (8-13 cancelled), 14, 15, 16, 17, 18, 19, 20, 21, 22 and 23. The restriction requirement set forth in the previous communication was based on the claims as numbered in the preliminary amendment (Paper No. 3), submitted August 13, 2001. However, the claims should have been renumbered prior to the restriction requirement. The original claims have now been renumbered in accordance with 37 CFR 1.126. The cancelled claims have been removed and the pending claims have been renumbered such that original claim 3 is now claim 2, original claim 5 is now claim 3, original claim 14 is now claim 6, and so forth (up to original claim 23 is now claim 15). Subsequent amendments to the claims included amendments to the originally cancelled claims (claims 2, 4, and 8-13). Cancelled claims cannot be amended, therefore, the claims submitted as amendments to the originally cancelled claims (claims 2, 4, and 8-13) have been entered as new claims 16, 17, 18, 19 and 20 (where the proposed amended claim 2 is now claim 16, the proposed amended claim 4 is now claim 17, and so forth). The claims proposed as new claims 14-22, therefore, needed to be renumbered as claims 19-29.

Claims 1-29 are now pending in the application.

Additionally, renumbered claim 3 is objected to because it now depends on a claim that has been renumbered as claim 17. It is improper for a dependent claim to precede the independent claim from which it depends.

Election/Restrictions

2. It is noted that the restriction was based on claims as numbered in the preliminary amendment filed August 13, 2001. As mentioned above, the claims a have been renumbered to comply with 37 CFR 1.126.

3. Applicant's election with traverse of Group I drawn to a shortened-chain 2'-5' polynucleotide (a group which encompasses renumbered claims 1-3, 6-20 and 23-26) in Paper No. 10 is acknowledged. The traversal is on the grounds that 1) The international stage of the instant application did not set forth a lack of unity of invention, 2) PCT Rule 13 permits inclusion of claims drawn to a process of making and a process of using a product, and 3) There is no serious search burden to search additional groups.

These arguments are not found persuasive. It is respectfully pointed out that 1) The results of the international stage of an application are non-binding, therefore, it is appropriate to find a lack of unity of invention in the national stage of an application even if a lack of unity was not set forth in the international stage; 2) There is no unity of invention, as evidenced by the reference cited below (see the rejection under 35 USC 102); therefore, restriction of products, processes of making and processes of using the products is appropriate; and 3) Search burden is not a criteria involved in analyzing applications filed under 35 USC 371 for restriction.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 4, 5, 21, 22, and 27-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3, 7-20 and 23-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a chain-shortened polynucleotide comprising phosphodiester bonds, wherein from about 0.1% to about 3% of the phosphodiester bonds are 2'-5' phosphodiester bonds. This claim is indefinite because the metes and bounds of the claim cannot be determined because of the vague limitations of **about** 0.1% to **about** 3%. Without specific limitations, the claims encompass polynucleotides that are contain less than 0.1% and greater than 3% 2'-5' phosphodiester bonds, as evidenced by the art rejections.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 1, 7, 10, 14, 16, 18, 19, 23, 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Guiying et al. (J. Med. Chem. Vol. 40: p. 1195-1200; 1997).

Guiying teaches a chain shortened polynucleotide comprising phosphodiester bonds, wherein from **about** 0.1 percent to **about** 3 percent of the phosphodiester bonds are 2'-5' phosphodiester bonds. It is noted that the limitation "about 3 percent" is vague and encompasses molecules comprising greater than 3 percent 2'-5' phosphodiester bonds, including molecules comprising about 9.5 percent 2'-5' phosphodiester bonds. Guiying teaches chimeric nucleic acid molecules of the general formula: p5'(A2'p)$_3$A2'p(CH$_2$)$_4$p(CH$_2$)$_4$p(5'N3'p)$_m$N, where N is any nucleoside and m is any integer (p. 1195, abstract). It is noted that the "A" in the formula refers to Adenosine (p. 1195, under "Introduction"), thus the molecules comprise polyadenylic acid, or an analogue thereof. This formula encompasses nucleic acid molecules of any size with an attached 2'-5'A sequence. Any such sequence greater than 133 nucleotides and less than 4000 nucleotides in length would constitute a sequence having between 0.1% and 3% 2'-5'phosphodiester linkages. Specifically, Guiying teaches an oligonucleotide (p5'A2'p5'A-

aPKR) which comprises a 2'-5'A moiety that has been shortened to just two nucleotides (p. 1195, footnote). This shortened oligonucleotide consists of a two nucleotide 2'-5'A attached to a 19mer oligonucleotide (p. 1195, footnote; and p. 1197, Table 2), which constitutes an oligonucleotide comprising 2 of 21 (or 9.5%) 2'-5' phosphodiester bonds. As mentioned above, the claim encompasses oligonucleotides comprising greater than 3% 2'-5' phosphodiester bonds, including an oligonucleotide comprising 9.5% 2'-5' phosphodiester bonds.

Guiying also teaches that the 2'-5'A oligonucleotides were added to cells in 5ml of fresh medium (p. 1199, under "Cell culture and Oligonucleotide treatment of Cells"). Treatment of the HeLa cells resulted in transfer of the oligonucleotides into the cells, as evidenced in Figure 1 (p. 1196). Therefore, the Guiying teaches composition comprising a carrier and said oligonucleotide complex wherein the carrier is effective for introducing the oligonucleotide into cells, wherein the oligonucleotide comprises 9.5% 2'-5'phosphodioester linkages and polyadenylic acid, or an analogue thereof. It is noted that "polyadenylic acid, or an analogue thereof" is a broad term that encompasses any nucleotide or nucleotide analogue as any nucleotide can be an analogue of adenosine.

9. Claims 1, 7, and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Kandimalla et al. (U.S. Patent 5,886,165, Filed Sept, 24, 1996).

Kandimalla teaches a chain shortened polynucleotide comprising phosphodiester bonds, wherein from **about** 0.1 percent to **about** 3 percent of the phosphodiester bonds are 2'-5' phosphodiester bonds. It is noted that the limitation "about 3 percent" is vague and encompasses molecules comprising greater than 3 percent 2'-5' phosphodiester bonds, including molecules

comprising about 9.5 percent 2'-5' phosphodiester bonds. Specifically, Kandimalla teaches oligonucleotides of any suitable length (column 3, line 62), but preferably from about 12 to about 50 nucleotides long (column 6, lines 8-10), and comprising at least two ribonucleotides connected via 2'-5' linkages, and the remainder are 3'-5' linked deoxyribonucleotides (column 3, lines 63-66). Kandimalla also teaches that the number of 2'-5' linked ribonucleotides can vary from two to all but two of the oligonucleotides' nucleotides (column 5, lines 66-67), confirming that the molecules only need to comprise two 2'-5' linkages. Therefore, Kandimalla teaches an oligonucleotide comprising 50 nucleotides of which two comprise 2'-5' linkages; this is an oligonucleotide that comprises 4% 2'-5' phosphodiester linkages (note that column 9, lines 35-37 teaches that SEQ ID NO. 2 and SEQ ID NO. 5 comprise 2'-5' phosphodiester linkages). As mentioned above, the claim encompasses oligonucleotides comprising greater than 3% 2'-5' phosphodiester bonds, including an oligonucleotide comprising 4% 2'-5'phosphodiester linkages.

Kandimalla teaches that the oligonucleotides comprise nucleotide bases selected from A, U, T, G, and C, and can comprise modified nucleotide bases. Therefore, the oligonucleotides can comprise polyadenylic acid or an analogue thereof. It is noted that "polyadenylic acid, or an analogue thereof" is a broad term that encompasses any nucleotide or nucleotide analogue as any nucleotide can be an analogue of adenosine.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 2, 3, 6, 8, 9, 15, 17, 20, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guiying et al. (J. Med. Chem. Vol. 40: p. 1195-1200; 1997) in view of Yano et al. (U.S. Patent 5,298,614) and further in view of Kandimalla et al (U.S. Patent 5,886,165).

Guiying teaches a chain shortened polynucleotide comprising phosphodiester bonds, wherein from **about** 0.1 percent to **about** 3 percent of the phosphodiester bonds are 2'-5' phosphodiester bonds. It is noted that the limitation "about 3 percent" is vague and encompasses molecules comprising greater than 3 percent 2'-5' phosphodiester bonds, including molecules comprising about 9.5 percent 2'-5' phosphodiester bonds. Guiying teaches chimeric nucleic acid molecules of the general formula: $p5'(A2'p)_3A2'p(CH_2)_4p(CH_2)_4p(5'N3'p)_mN$, where N is any nucleoside and m is any integer (p. 1195, abstract). It is noted that the "A" in the formula refers to Adenosine (p. 1195, under "Introduction"), thus the molecules comprise polyadenylic acid, or an analogue thereof. This formula encompasses nucleic acid molecules of any size with an

attached 2'-5'A sequence. Any such sequence greater than 133 nucleotides and less than 4000 nucleotides in length would constitute a sequence having between 0.1% and 3% 2'-5'phosphodiester linkages. Specifically, Guiying teaches an oligonucleotide (p5'A2'p5'A-aPKR) which comprises a 2'-5'A moiety that has been shortened to just two nucleotides (p. 1195, footnote). This shortened oligonucleotide consists of a two-nucleotide 2'-5'A attached to a 19mer oligonucleotide (p. 1195, footnote; and p. 1197, Table 2), which constitutes an oligonucleotide comprising 2 of 21 (or 9.5%) 2'-5' phosphodiester bonds. As mentioned above, the claim encompasses oligonucleotides comprising greater than 3% 2'-5' phosphodiester bonds, including an oligonucleotide comprising 9.5% 2'-5' phosphodiester bonds.

Guiying also teaches that the 2'-5'A oligonucleotides were added to cells in 5ml of fresh medium (p. 1199, under "Cell culture and Oligonucleotide treatment of Cells"). Treatment of the HeLa cells resulted in transfer of the oligonucleotides into the cells, as evidenced in Figure 1 (p. 1196). Therefore, the Guiying teaches composition comprising a carrier and said oligonucleotide complex wherein the carrier is effective for introducing the oligonucleotide into cells, wherein the oligonucleotide comprises 9.5% 2'-5'phosphodioester linkages and polyadenylic acid, or an analogue thereof. It is noted that "polyadenylic acid, or an analogue thereof" is a broad term that encompasses any nucleotide or nucleotide analogue as any nucleotide can be an analogue of adenosine.

Guiying does not teach that the oligonucleotide is double stranded or in the range of 0.1kb to about 1kb.

Yano teaches a double stranded nucleic acid molecule that are from 50 to 10,000 base pairs in length and are comprised of polyinosinic acid (poly I) and polycytidylic acid (poly C)

forming a poly I:polyC substance that has activities such as Interferon inducing action, proliferation inhibiting action for tumor cells, and immune system activating action in vivo, and are therefore useful in antiviral and anticancer treatment (column 3, lines 1-50). Yano also teaches the chain length is generally from 100 to 600 base numbers (column 11, lines 33-34), which constitute molecules the range of 0.1kb to about 1kb.

Kandimalla teaches a mixed base oligonucleotide comprising 2'-5' and 3'-5' internucleotide linkages and teaches that the addition of the 2'-5'-linked oligonucleotides results in an oligonucleotide with a "higher stability against various exonucleases... as compared to 3'-5'-linked oligonucleotides" (column 5 lines 10-13).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make the double stranded poly I:poly C immune inducing/cancer treating agent of Yano with a 2'-5'polyadenylate linkage of Guiying to produce a double stranded poly I:poly C molecule comprising 0.1%-3% 2'-5'polyA linkages and are in the range of 0.1kb to about 1kb in length. The motivation to make such a molecule is to construct a therapeutic molecule (taught by Yano) comprising about 0.1%-3% 2'-5'polyA linkages (taught by Guiying), thus conferring a higher stability to the molecule, as taught by Kandimalla. It would have been obvious to the ordinary artisan that increasing the stability of a therapeutic compound could increase therapeutic effectiveness. Guiying teaches chimeric nucleic acid molecules of the general formula: $p5'(A2'p)_3A2'p(CH_2)_4p(CH_2)_4p(5'N3'p)_mN$, where N is any nucleoside and m is any integer (p. 1195, abstract); therefore, one of ordinary skill in the art could combine the teachings of Guiying and Yano, with a reasonable expectation of success.

13. Claims 11 and 12, rejected under 35 U.S.C. 103(a) as being unpatentable over Guiying et al. (J. Med. Chem. Vol. 40: p. 1195-1200; 1997) in view of Yano et al. (U.S. Patent 5,298,614) and further in view of Kandimalla et al (U.S. Patent 5,886,165) and Gao et al. (U.S. Patent 5,795,587).

Guiying teaches a chain shortened polynucleotide comprising phosphodiester bonds, wherein from **about** 0.1 percent to **about** 3 percent of the phosphodiester bonds are 2'-5' phosphodiester bonds. It is noted that the limitation "about 3 percent" is vague and encompasses molecules comprising greater than 3 percent 2'-5' phosphodiester bonds, including molecules comprising about 9.5 percent 2'-5' phosphodiester bonds. Guiying teaches chimeric nucleic acid molecules of the general formula: p5'(A2'p)$_3$A2'p(CH$_2$)$_4$p(CH$_2$)$_4$p(5'N3'p)$_m$N, where N is any nucleoside and m is any integer (p. 1195, abstract). It is noted that the "A" in the formula refers to Adenosine (p. 1195, under "Introduction"), thus the molecules comprise polyadenylic acid, or an analogue thereof. This formula encompasses nucleic acid molecules of any size with an attached 2'-5'A sequence. Any such sequence greater than 133 nucleotides and less than 4000 nucleotides in length would constitute a sequence having between 0.1% and 3% 2'-5'phosphodiester linkages. Specifically, Guiying teaches an oligonucleotide (p5'A2'p5'A-aPKR) which comprises a 2'-5'A moiety that has been shortened to just two nucleotides (p. 1195, footnote). This shortened oligonucleotide consists of a two-nucleotide 2'-5'A attached to a 19mer oligonucleotide (p. 1195, footnote; and p. 1197, Table 2), which constitutes an oligonucleotide comprising 2 of 21 (or 9.5%) 2'-5' phosphodiester bonds. As mentioned above, the claim encompasses oligonucleotides comprising greater than 3% 2'-5' phosphodiester bonds, including an oligonucleotide comprising 9.5% 2'-5' phosphodiester bonds.

Guiying also teaches that the 2'-5'A oligonucleotides were added to cells in 5ml of fresh medium (p. 1199, under "Cell culture and Oligonucleotide treatment of Cells"). Treatment of the HeLa cells resulted in transfer of the oligonucleotides into the cells, as evidenced in Figure 1 (p. 1196). Therefore, the Guiying teaches composition comprising a carrier and said oligonucleotide complex wherein the carrier is effective for introducing the oligonucleotide into cells, wherein the oligonucleotide comprises 9.5% 2'-5'phosphodioester linkages and polyadenylic acid, or an analogue thereof. It is noted that "polyadenylic acid, or an analogue thereof" is a broad term that encompasses any nucleotide or nucleotide analogue as any nucleotide can be an analogue of adenosine.

Guiying does not teach that the oligonucleotide is double stranded or in the range of 0.1kb to about 1kb.

Yano teaches a double stranded nucleic acid molecule that are from 50 to 10,000 base pairs in length and are comprised of polyinosinic acid (poly I) and polycytidylic acid (poly C) forming a poly I:polyC substance that has activities such as Interferon inducing action, proliferation inhibiting action for tumor cells, and immune system activating action in vivo, and are therefore useful in antiviral and anticancer treatment (column 3, lines 1-50). Yano also teaches the chain length is generally from 100 to 600 base numbers (column 11, lines 33-34), which constitute molecules the range of 0.1kb to about 1kb.

Kandimalla teaches a mixed base oligonucleotide comprising 2'-5' and 3'-5' internucleotide linkages and teaches that the addition of the 2'-5'-linked oligonucleotides results in an oligonucleotide with a "higher stability against various exonucleases... as compared to 3'-5'-linked oligonucleotides" (column 5 lines 10-13).

Guiying, Yano and Kandimalla do not teach a composition comprising a positively charged carrier (such as a cationic liposome) complexed to the oligonucleotide.

Gao teaches that cationic lipids (which constitute a positively charged carrier) can be used as vehicles for the transfer of nucleic acids or other molecules such as proteins into cells (column 1, lines 5-12). Gao specifically teaches that "the macromolecules which are particularly suitable for use with the complexes of the invention [cationic liposomes] are for example, DNA, RNA, oligonucleotides or negatively charged proteins." (Column 3, lines 5-10). Gao also indicates steps for making the complex comprising nucleic acids and cationic liposome carrier (column 5, lines 13-65).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a double stranded poly I:poly C molecule that has a size of 0.1kb to about 1kb in length and comprises about 0.1%-3% 2'-5'A linkages and is complexed to a positively charged, cationic liposome with a reasonable expectation of success. The motivation to make such a complex is provided by Yano, Guiying, Kandimalla and Gao. Yano, Guiying and Kandimalla teach that it would be desirable to deliver the molecule to cells for therapeutic purposes, as mentioned above, and Gao teaches that the cationic liposome can be complexed to nucleic acids and used to deliver the nucleic acid into cells.

14. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guiying et al. (J. Med. Chem. Vol. 40: p. 1195-1200; 1997) in view of Yano et al. (U.S. Patent 5,298,614) and further in view of Kandimalla et al (U.S. Patent 5,886,165) and Junichi et al. (U.S. Patent 6,020,317).

Guiying teaches a chain shortened polynucleotide comprising phosphodiester bonds, wherein from **about** 0.1 percent to **about** 3 percent of the phosphodiester bonds are 2'-5' phosphodiester bonds. It is noted that the limitation "about 3 percent" is vague and encompasses molecules comprising greater than 3 percent 2'-5' phosphodiester bonds, including molecules comprising about 9.5 percent 2'-5' phosphodiester bonds. Guiying teaches chimeric nucleic acid molecules of the general formula: $p5'(A2'p)_3A2'p(CH_2)_4p(CH_2)_4p(5'N3'p)_mN$, where N is any nucleoside and m is any integer (p. 1195, abstract). It is noted that the "A" in the formula refers to Adenosine (p. 1195, under "Introduction"), thus the molecules comprise polyadenylic acid, or an analogue thereof. This formula encompasses nucleic acid molecules of any size with an attached 2'-5'A sequence. Any such sequence greater than 133 nucleotides and less than 4000 nucleotides in length would constitute a sequence having between 0.1% and 3% 2'-5'phosphodiester linkages. Specifically, Guiying teaches an oligonucleotide (p5'A2'p5'A-aPKR) which comprises a 2'-5'A moiety that has been shortened to just two nucleotides (p. 1195, footnote). This shortened oligonucleotide consists of a two-nucleotide 2'-5'A attached to a 19mer oligonucleotide (p. 1195, footnote; and p. 1197, Table 2), which constitutes an oligonucleotide comprising 2 of 21 (or 9.5%) 2'-5' phosphodiester bonds. As mentioned above, the claim encompasses oligonucleotides comprising greater than 3% 2'-5' phosphodiester bonds, including an oligonucleotide comprising 9.5% 2'-5' phosphodiester bonds.

Guiying also teaches that the 2'-5'A oligonucleotides were added to cells in 5ml of fresh medium (p. 1199, under "Cell culture and Oligonucleotide treatment of Cells"). Treatment of the HeLa cells resulted in transfer of the oligonucleotides into the cells, as evidenced in Figure 1 (p. 1196). Therefore, the Guiying teaches composition comprising a carrier and said

oligonucleotide complex wherein the carrier is effective for introducing the oligonucleotide into cells, wherein the oligonucleotide comprises 9.5% 2'-5'phosphodioester linkages and polyadenylic acid, or an analogue thereof. It is noted that "polyadenylic acid, or an analogue thereof" is a broad term that encompasses any nucleotide or nucleotide analogue as any nucleotide can be an analogue of adenosine.

Guiying does not teach that the oligonucleotide is double stranded or in the range of 0.1kb to about 1kb.

Yano teaches a double stranded nucleic acid molecule that are from 50 to 10,000 base pairs in length and are comprised of polyinosinic acid (poly I) and polycytidylic acid (poly C) forming a poly I:polyC substance that has activities such as Interferon inducing action, proliferation inhibiting action for tumor cells, and immune system activating action in vivo, and are therefore useful in antiviral and anticancer treatment (column 3, lines 1-50). Yano also teaches the chain length is generally from 100 to 600 base numbers (column 11, lines 33-34), which constitute molecules the range of 0.1kb to about 1kb.

Kandimalla teaches a mixed base oligonucleotide comprising 2'-5' and 3'-5' internucleotide linkages and teaches that the addition of the 2'-5'-linked oligonucleotides results in an oligonucleotide with a "higher stability against various exonucleases... as compared to 3'-5'-linked oligonucleotides" (column 5 lines 10-13).

Guiying, Yano and Kandimalla do not teach a composition comprising a positively charged carrier (such as a cationic liposome) complexed to the oligonucleotide.

Gao teaches that cationic lipids (which constitute a positively charged carrier) can be used as vehicles for the transfer of nucleic acids or other molecules such as proteins into cells

(column 1, lines 5-12). Gao specifically teaches that "the macromolecules which are particularly suitable for use with the complexes of the invention [cationic liposomes] are for example, DNA, RNA, oligonucleotides or negatively charged proteins." (Column 3, lines 5-10). Gao also indicates steps for making the complex comprising nucleic acids and cationic liposome carrier (column 5, lines 13-65).

Junichi teaches a lipid compound that is functionally equivalent to cationic liposome and has a lower toxicity. The compound taught by Junichi includes 2-O-(2-diethylaminoethyl) carbamoyl-1,3-O-dioleylglycerol and a phospholipid (see abstract). Junichi indicates that the compound is useful for delivering double stranded nucleic acid to cells (see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a double stranded poly I:poly C molecule that has a size of 0.1kb to about 1kb in length and comprises about 0.1%-3% 2'-5'A linkages and is complexed to 2-O-(2-diethylaminoethyl) carbamoyl-1,3-O-dioleylglycerol and a phospholipid with a reasonable expectation of success.

The motivation to make such a complex is provided by Yano, Guiying, Kandimalla and Junichi. Yano, Guiying and Kandimalla teach that it would be desirable to deliver the molecule to cells for therapeutic purposes, as mentioned above, and Junichi teaches that the 2-O-(2-diethylaminoethyl) carbamoyl-1,3-O-dioleylglycerol and a phospholipid can be complexed to double stranded nucleic acids and used to deliver the nucleic acid to cells. Furthermore Junichi teaches that the double strand nucleic acid/2-O-(2-diethylaminoethyl) carbamoyl-1,3-O-dioleylglycerol/phospholipid complex is useful for delivering the double stranded nucleic acid to cells (see abstract).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
July 1, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER